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*Original Article*

# FORMULATION AND EVALUATION OF GASTRO-RETENTIVE IN-SITU GEL OF ANTI-ULCER DRUG MISOPROSTOL

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**ABSTRACT**

**Background:** Peptic ulcer disease (PUD) is a prevalent gastrointestinal disorder caused by an imbalance between protective and aggressive gastric factors. Misoprostol, a synthetic prostaglandin E1 analogue, is effective in ulcer management but has limitations such as rapid metabolism, low bioavailability, and frequent dosing. This study aimed to develop a gastro-retentive in-situ gel of misoprostol to enhance gastric retention and controlled drug release. **Methods:** The in-situ gel was formulated using gellan gum and calcium carbonate as key excipients. A $3^2$ factorial design was employed to optimize floating lag time and in-vitro drug release. The formulations were evaluated for pH, viscosity, gelling capacity, floating behavior, drug content, and in-vitro drug release using a USP Type II dissolution apparatus in simulated gastric fluid (pH 1.2). Stability studies were conducted under accelerated conditions (40°C ± 2°C / 75% ± 5% RH) for six months. **Results:** The optimized formulation (LF5) exhibited a pH of 6.6, a floating lag time of 18.03 seconds, and a total floating time exceeding 6 hours, ensuring prolonged gastric retention. Drug content analysis confirmed 93.04% uniformity across batches. In-vitro drug release showed sustained drug release of 93.04% over 240 minutes. Stability studies demonstrated no significant changes in pH, floating behavior, or drug content, confirming formulation robustness. **Conclusion:** The gastro-retentive in-situ gel of misoprostol successfully enhanced gastric retention and controlled drug release. The optimized formulation exhibited rapid buoyancy, prolonged retention, and stability, making it a promising approach for improving misoprostol's therapeutic efficacy in peptic ulcer management.

**KEYWORDS:** Peptic ulcer disease, Gastro-retentive in-situ gel, Misoprostol, Gellan gum, Calcium carbonate, Floating drug delivery, Controlled release, Stability study.



## 1. Introduction

Peptic ulcer disease (PUD) is a common gastrointestinal ailment that is characterized by the presence of open sores in the mucosa of the stomach and/or the first part of the small intestine. Such ulcers develop because of the imbalance of several factors that include mucus and bicarbonate production, and injurious factors that involve gastric acid, pepsin, and bacterial agents [1]. PUD mostly arises as a result of *Helicobacter pylori* infection and utilization of non-steroidal anti-inflammatory drugs (NSAIDs), which cause the wearing out of the stomach lining. High consumption of spices, smoking, alcohol, stress and irregular mealtimes are among the other practices which might lead to ulcer formation [2]. PUD may present as mild or severe and can be fatal; the main features include epigastric burning pain, fullness, nausea, vomiting, anorexia and weight loss. In some severe cases, it may cause haemorrhagic ulcers and may manifest as vomiting of blood or passing black-coloured stool due to gastrointestinal bleeding [3]. Unfortunately, the global incidence of PUD has remained high and is estimated to

affect millions of people across the world every year [4]. Epidemiological research carried out in the recent past revealed that peptic ulcers affect about 8 to 10 percent of inhabitants across the world at some point in their lifetime. About 4 to 5 new cases are reported annually, and many of the cases result in hospitalization [5]. Complications arising from this ailment lead to a high mortality rate, and estimates indicate that about 15,000-20,000 people die due to bleeding or perforated ulcers. According to the present study, potential methods to alleviate the persistence of ulcers are still a point of concern due to medical treatment breakthroughs [6].

Over the last decades, in-situ gel-based drug delivery systems have become an attractive form of new therapeutic technique used in the treatment of PUD [7]. These systems are based on formulations that are in a liquid state at some point and are then able to form a gel under certain physiological conditions, such as temperature [8], pH and ionic concentrations. This leads to the drug staying within the stomach for a longer time by making it float, thus delaying its departure into the intestines [8]. The in-situ gel system has some advantages over the conventional dosage form, like tablets and capsules, where the drug has the following merits: increased bioavailability, less frequent dosing, and a mucoadhesive property which allows adequate contact between the drug and the mucous membrane of the stomach [9]. Designed to release a drug in the stomach and prevent its rapid absorption, the in-situ gels improve the drug's therapeutic effect and reduce the side effects. This approach is widely effective for anti-ulcer drugs because they have an opportunity to act constantly and locally at the site of the ulcers, thus helping to reduce the time that is taken to heal the ulcers as well as preventing the recurrence of the ulcers [9].

Misoprostol is a synthetic prostaglandin E1 (PGE1) analogue that is effective for the management and prophylaxis of NSAID-associated gastroduodenal ulcers [10]. It is important in the gastric mucosa protection through promoting mucus and bicarbonate production, increasing blood flow to the mucosa, and decreasing gastric acid output. The pharmacology of misoprostol is unique from that of other acid control drugs like proton pump inhibitors and H2-receptor antagonists because misoprostol directly stimulates an increase in resistance of the gastric mucosa lining [11]. Nonetheless, there are three disadvantages of using misoprostol in its oral formulation, namely, rapid metabolism, low bioavailability, and common side effects like diarrhoea and abdominal cramps. Also, its conventional dosage forms entail frequent dosing, and this may not be a factor that aligns with patients' adherence [12]. To overcome these limitations, the development of a gastro-retentive in-situ gel formulation for misoprostol is an appropriate approach [13]. It would not only augment the stability of the drug in the stomach environment, but it would also make the release and functioning of the drug time-sustained and controlled, thus improving the efficiency of the drug in treatment as well as the continued use by the patient. When misoprostol is formulated in an in-situ gel system, the positive effects on the gastrointestinal tract are felt, while there are negligible side effects as compared to conventional formulations [14].

The purpose of the present investigation was to design and develop an in-situ gel formulation for the controlled release of misoprostol. To achieve this, we planned for a formulation that transforms itself into a gel in the presence of gastric fluids, therefore improving the stability of the drug, its retention time in the stomach, and the release rate. Thus, it is believed that the frequency of administration of misoprostol will be decreased in the realm of treating PUD, with a decrease in side effects.

## 2. Materials and methods

### 2.1. Materials

Misoprostol was procured from Sciquaint Innovations (OPC) Pvt. Ltd., Pune. Gellan gum, carbopol 934, and propyl paraben were purchased from Research Fine Chem Laboratories, Mumbai, India. Sodium citrate was obtained from Citreos, while calcium chloride was sourced from Logogens, India. Calcium carbonate was procured from Chemigens, Mumbai, India. All chemicals and reagents used in the study were of analytical grade, and deionized water was used throughout the formulation and experimental procedures to ensure consistency and accuracy.

### 2.2.1. Calibration curve of misoprostol

The calibration curve of misoprostol was prepared using ethanol as a solvent for the preparation of the standard solutions. The stock solution was prepared from 10 mg of pure misoprostol in a 100 ml volumetric flask, which was then diluted with ethanol to yield a concentration of 100 µg/ml. From the stock solution, 5, 10, 15, 20, 25 and 30 ppm solutions were prepared. The absorbance of these solutions was measured on a Shimadzu UV-1900 UV-Visible spectrophotometer at 207 nm, which was determined as $\lambda_{max}$ for misoprostol. A calibration curve was developed by plotting absorbance against concentration [15].

### 2.2.2. Determination of solubility

The saturated solubility study of misoprostol was conducted in various solvents, including water, ethanol, 0.1 M phosphate buffer (pH 6.8), and dimethyl sulfoxide (DMSO), to assess its solubility profile under physiological and formulation-relevant conditions. Excess amounts of misoprostol were added to 50 ml of each solvent in separate 100 ml volumetric flasks, ensuring saturation equilibrium. The flasks were hermetically sealed and placed in an orbital-shaking water bath set at 50 rpm and maintained at a controlled temperature of 37 ± 0.5°C for 48 hours to facilitate solubilization and equilibrium attainment. Following the equilibration period, the solutions were filtered to remove any undissolved drug particles, and the filtrates were appropriately diluted with their respective solvents. The drug concentration in each medium was determined using a UV-visible spectrophotometer (Shimadzu UV-1900) at a wavelength of 207 nm. The absorbance values obtained were converted into concentrations using the standard calibration curve of misoprostol [16].

### 2.2.3. FTIR spectroscopy

The Fourier Transform Infrared (FTIR) Spectroscopy analysis of misoprostol and its physical mixture was performed using a Jasco 4600 IR spectrophotometer to evaluate the functional groups and possible interactions within the formulation. The instrument operated on the diffuse reflectance principle in combination with the

potassium bromide (KBr) pellet method, ensuring optimal spectral resolution. The spectra were recorded within the wavenumber range of 4000–400 $cm^{-1}$, allowing for the identification of characteristic peaks corresponding to various functional groups present in the drug and formulation components. This analysis aids in confirming the structural integrity of misoprostol and assessing any potential chemical interactions between the drug and excipients [16].

### 2.2.4. Differential Scanning Colorimetry (DSC)

The Differential Scanning Calorimetry (DSC) analysis of pure misoprostol and its physical mixture was conducted using a Perkin-Elmer Pyris-1 DSC instrument (Osaka, Japan) to assess the thermal behavior and potential interactions between the drug and excipients. Before analysis, moisture was removed by preheating the samples to eliminate any residual water content. Precisely 5 mg of each sample was accurately weighed and placed in a 40 µL aluminum pan, which was hermetically sealed to prevent environmental influences, while alpha alumina powder was used as the reference material. The thermograms were recorded over a temperature range of 50°C to 300°C at a controlled heating rate of 20°C/min under a continuous flow of nitrogen gas (20 ml/min) to maintain an inert atmosphere and prevent oxidative degradation. The DSC thermograms were analyzed to determine exothermic and endothermic peak positions, allowing for the identification of characteristic melting transitions and potential alterations in thermal properties [17].

### 2.2.5. Experimental design

A full factorial 32 design was employed to systematically evaluate the influence of gellan gum ($X_1$) and calcium carbonate ($X_2$) on the formulation's performance [18]. Both independent variables were studied at three concentration levels (0.5%, 1.0%, and 1.5% w/v and 1%, 1.5% and 2% w/v, respectively) to assess their impact on key formulation characteristics. The dependent variables analyzed included floating lag time (Y1) and percentage in-vitro drug release (Y2). The experimental design and statistical optimization were conducted using Design-Expert software (Stat-Ease version 13.0). A total of nine experimental batches were prepared based on the factorial design and presented in Tables 1 – 3.

**Table 1.** $3^2$ Factorial Design showing independent factors and levels.

| Independent Variables | | | | |
|---|---|---|---|---|
| Label | Factors | Level (% w/v) | | |
| | | Low (-) | Medium | High (+) |
| A | Gellan gum | 0.5 | 1 | 1.5 |
| B | Calcium carbonate | 1 | 1.5 | 2 |
| **Dependant Variables** | | | | |
| $Y_1$ | Floating lag time (s) | | | |
| Y2 | *In-vitro* drug release (%) | | | |

**Table 2.** Factors, levels and responses taken in $3^2$ complete factorial designs for gastro-retentive in-situ gel.

| Formulation Code | (A) | (B) |
|---|---|---|
| F1 | -1 | -1 |
| F2 | 0 | -1 |
| F3 | +1 | -1 |
| F4 | -1 | 0 |
| F5 | 0 | 0 |
| F6 | +1 | 0 |
| F7 | -1 | +1 |
| F8 | 0 | +1 |
| F9 | +1 | +1 |

### 2.2.6. Formulation of gastroretentive in-situ gel

The gastro-retentive in-situ gel was formulated by dissolving misoprostol in 50 ml of deionized water [19]. Calcium carbonate was then added as a gas-generating agent under continuous stirring. A separate solution of gellan gum was prepared by dissolving it in 100 ml of deionized water containing sodium citrate and calcium chloride, heated to 60°C, and stirred until complete dispersion. After cooling to below 40°C, this solution was added to the misoprostol mixture while stirring to ensure uniform dispersion. Finally, a carbopol 934 and methylparaben solution was incorporated and mixed thoroughly. The final volume was adjusted, and the formulation was stored in amber-colored bottles until further evaluation [20].

**Table 3.** Preparation of gastro-retentive in-situ gel batches using $3^2$ factorial designs.

| Ingredients | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
|---|---|---|---|---|---|---|---|---|---|
| Misoprostol (µg) | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 800 | 800 |
| Gellan gum (% w/v) | 0.5 | 1 | 1.5 | 0.5 | 1 | 1.5 | 0.5 | 1 | 1.5 |
| Calcium carbonate (% w/v) | 1 | 1 | 1 | 1.5 | 1.5 | 1.5 | 2 | 2 | 2 |
| Sodium citrate (% w/v) | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 | 0.5 |
| Calcium chloride (% w/v) | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 | 0.15 |
| Propyl paraben (% w/v) | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Deionized water q.s to 100 ml | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |

**2.2.7. Characterization of gastro-retentive in-situ gel**

**2.2.7.1. Determination of pH**

The pH determination of the misoprostol gastro-retentive in-situ gel was conducted to ensure compatibility with gastric conditions and formulation stability. The pH of the prepared in-situ gel formulations was measured using a Lab India Digital pH Meter (Model: PICO+). A 10 ml sample of the formulation was accurately transferred into a beaker, and the electrode of the pH meter was immersed into the sample at room temperature. The readings were recorded once the values stabilized, and measurements were performed in triplicate to ensure accuracy [21].

**2.2.7.2. Floating lag time**

The floating lag time of the gastro-retentive in-situ gel formulation of misoprostol was evaluated using an in-vitro buoyancy study conducted in a USP Type II dissolution apparatus (Electrolab, India). The dissolution medium consisted of 0.1 N hydrochloric acid (pH 1.2), maintained at 37°C ± 0.5°C to simulate gastric conditions. A 10 ml sample of the prepared in-situ gel formulation was introduced into the medium, and the time taken for the gel to begin floating (floating lag time) was recorded in seconds [22].

**2.2.7.3. Total floating time**

The total floating time of the misoprostol gastro-retentive in-situ gel was evaluated using a USP dissolution apparatus II containing 900 ml of 0.1 N HCl as the dissolution medium. The temperature was maintained at 37 ± 0.5°C, and 10 ml of the prepared in-situ gel formulation was introduced into the medium. The duration for which the formulation remained afloat (total floating time) was recorded. This test was conducted to ensure that the formulation exhibits a prolonged gastric retention time, which is essential for effective drug release and therapeutic efficacy [23].

**2.2.7.4. Determination of drug content**

The drug content of the misoprostol gastro-retentive in-situ gel was determined using a UV-visible spectrophotometric assay. A specific amount (1 ml) of the in-situ gel formulation was dissolved in 100 ml of simulated gastric fluid (0.1 N HCl, pH 1.2) and stirred for 30 minutes to ensure complete drug extraction. The solution was then filtered through a 0.45 µm membrane filter to remove any particulate matter. The absorbance of the filtrate was measured at 207 nm using a Shimadzu UV-1900 spectrophotometer, and the drug concentration was calculated using the misoprostol standard calibration curve. The experiment was performed in triplicate. This method ensured accurate quantification of misoprostol in the formulation, confirming drug uniformity and content consistency across different batches [24].

**2.2.7.5. Determination of viscosity**

The viscosity of the formulated in-situ gel was measured using a Brookfield Digital Rheometer DV-III equipped with a CP-52 cone and plate spindle. A sample volume of 10 ml of the prepared sol was transferred into a Petri dish with an internal diameter of 27 mm. The Petri dish containing the sample was carefully placed in 900 ml of 0.1 N HCl maintained at 37°C for 10 minutes to allow gel formation. After the gel was formed, the viscosity values were recorded using the rheometer at different rotational speeds. The measurement was conducted under controlled temperature conditions to ensure accuracy. The viscosity assessment was crucial in determining the gel's mechanical properties, which directly influence its gastro-retentive performance and drug release profile [25].

**2.2.7.6. Gelling capacity of formulations**

The gelling capacity of the misoprostol gastro-retentive in-situ gel was evaluated to assess its ability to transition from a sol (liquid) state to a gel upon exposure to gastric conditions. A specific volume (10 ml) of the prepared in-situ gel formulation was added to 900 ml of simulated gastric fluid (0.1 N HCl, pH 1.2) maintained at 37 ± 0.5°C in a USP dissolution apparatus II. The transformation of the sol into a gel was visually observed, and the gel strength and integrity were evaluated over time. The formulations were categorized based on their gelling capacity: (+) weak gelation with fast dissolution, (++) moderate gelation with retained structure for a few hours, and (+++) strong gelation with prolonged stability and resistance to gastric motility. The test confirmed the ability of the misoprostol in-situ gel to form a stable gel in the stomach, ensuring prolonged retention, controlled drug release, and effective gastro-retentive performance [26].

**2.2.7.7. In-vitro drug release study**

The in-vitro drug release study for the misoprostol gastro-retentive in-situ gel was conducted using a USP Type II Dissolution Apparatus to evaluate the sustained drug release profile [27]. A 10 ml sample of the in-situ gel formulation was accurately transferred into a dissolution vessel containing 900 ml of 0.1 N HCl (pH 1.2), maintained at 37 ± 0.5°C with a stirring speed of 50 rpm to simulate gastric conditions. At predetermined time intervals, 5 ml aliquots were withdrawn and immediately replaced with an equal volume of fresh pre-warmed dissolution medium to maintain sink conditions. The withdrawn samples were filtered through a 0.45 µm membrane filter, and drug concentrations were determined using a UV-visible spectrophotometer (Shimadzu UV-1900) at 207 nm, based on the established calibration curve of misoprostol. The cumulative drug release was plotted against time to analyze the release kinetics. This study was conducted in triplicate, and results were expressed as mean ± standard deviation, ensuring accuracy and reproducibility of the sustained release formulation [28].

**2.2.7.8. Stability study**

The stability study of the misoprostol gastro-retentive in-situ gel was conducted to assess its physical and chemical stability under controlled conditions. The formulation was stored at accelerated conditions (40°C ± 2°C / 75% ± 5% RH) and real-time conditions (25°C ± 2°C / 60% ± 5% RH) for up to three months, with samples withdrawn at 1st, 15th, 30th, 60th, 90th and 180th days [29]. The stability parameters evaluated included appearance, pH, viscosity, drug content, in-vitro drug release profile, floating lag time, and total floating time. Physical stability was assessed by observing changes in color, odor, and phase separation, while pH measurements ensured no significant deviation affecting drug solubility and gelation properties. The viscosity was analyzed using a Brookfield Digital Rheometer to monitor consistency and gelling behavior. Chemical stability was confirmed by drug content analysis

using a UV-visible spectrophotometer (Shimadzu UV-1900) at 207 nm, ensuring potency remained within acceptable limits. Additionally, the in-vitro drug release profile was evaluated at each time point to detect any deviations from the initial release pattern. Floating lag time and total floating time were measured to ensure the formulation maintained its buoyancy [26].

## 3. Results

### 3.1. Results of the calibration curve of misoprostol

The calibration curve of misoprostol in ethanol exhibited a linear relationship between absorbance and concentration, with a high correlation coefficient ($R^2$ = 0.9987) as indicated in Fig. 1.

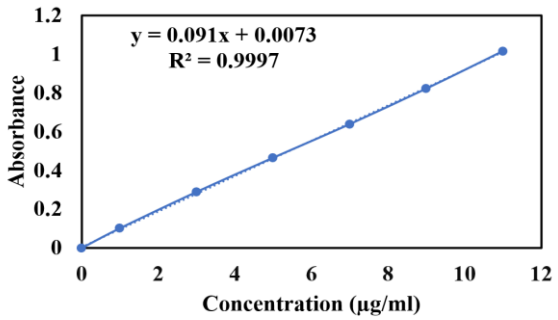


**Fig. 1**. Calibration curve of misoprostol in ethanol.

### 3.2 Solubility study

The solubility study of misoprostol in different solvents revealed significant variations. The obtained results are presented in Table 4. In water, misoprostol exhibited practically insoluble behavior, indicating poor aqueous solubility that may affect bioavailability. In contrast, it was soluble in ethanol and DMSO, suggesting their suitability for formulations requiring enhanced solubility. In phosphate buffer (pH 6.8), the drug showed slightly soluble characteristics, indicating limited solubility at physiological pH, which may influence drug release. Overall, ethanol and DMSO proved to be effective solvents for dissolving misoprostol, while its poor aqueous solubility highlights the need for solubility enhancement strategies in pharmaceutical formulations.

**Table 4.** Results of solubility analysis of misoprostol.

| Sr. No. | Solvent | Solubility (mg/ml) | Results |
|---|---|---|---|
| 1 | Water | 0.023±0.002 | Practically insoluble |
| 2 | Ethanol | 49.36±2.72 | Soluble |
| 3 | Phosphate Buffer pH 6.8 | 1.63±0.41 | Slightly soluble |
| 4 | DMSO | 50.87±2.29 | Soluble |

### 3.3. Results of FTIR

The FTIR spectrum of pure misoprostol exhibited characteristic peaks at 3435 $cm^{-1}$ (-OH stretching), 1732 $cm^{-1}$ (C=O stretching), and 1256 $cm^{-1}$ (-O- stretching), confirming its structural integrity. In the physical mixture, these peaks remained largely unchanged, with only minor shifts observed, suggesting no significant chemical interactions between misoprostol and the excipients. Additionally, the absence of new peaks indicates that misoprostol remains chemically stable within the formulation, ensuring its therapeutic efficacy. These results confirm the compatibility of the selected excipients, preserving the drug's functional groups. Results of FTIR study are indicated in Fig. 2 and 3.

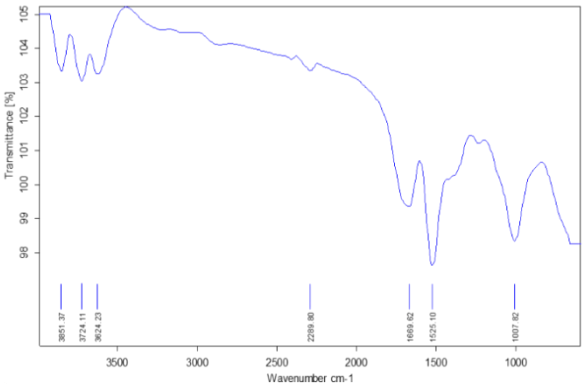


**Fig. 2**. FTIR spectra of pure drug (misoprostol).

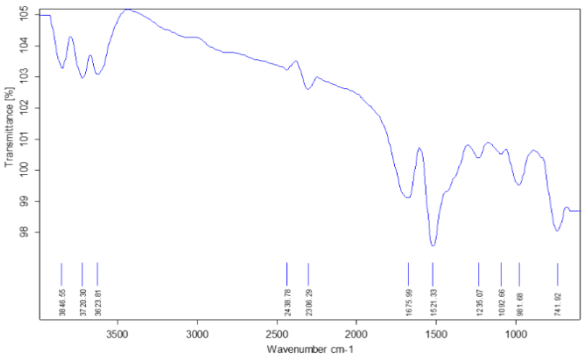


**Fig. 3**. FTIR spectra of physical mixture (drug + excipients).

### 3.4. Results of DSC analysis

The DSC thermogram of pure misoprostol (Fig. 4) exhibited a sharp endothermic peak at 163.07°C, confirming its crystalline nature and thermal stability. In the physical mixture (Fig. 5), two additional peaks were observed at 90°C and 262°C, indicating partial interaction between misoprostol and the excipients, likely due to the melting of excipient components and slight modifications in the drug's thermal behaviour. However, the retention of the characteristic peak at 163.07°C suggests that misoprostol's crystalline structure remains largely intact. These findings confirm the compatibility of the selected excipients and ensure the stability of the developed gastro-retentive in-situ gel formulation.

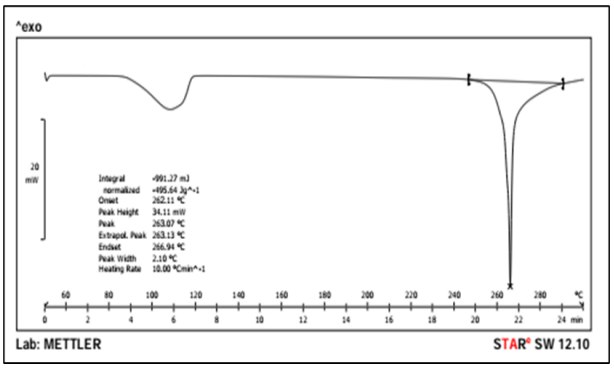


**Fig. 4.** DSC spectra of misoprostol.

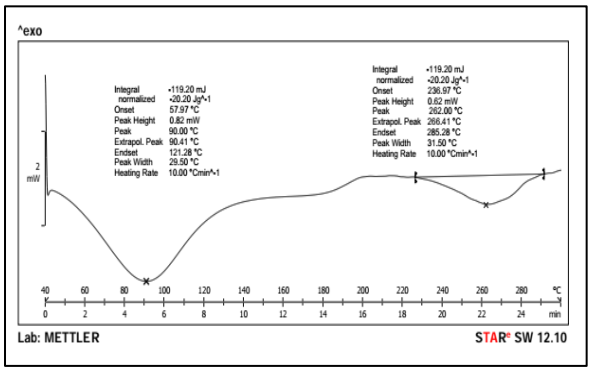


**Fig. 5.** DSC spectra of physical mixture (drug + excipients).

### 3.5. Results of physical appearance, gelling capacity and viscosity determination

The evaluation of gelling capacity, viscosity, floating behavior, and drug content revealed significant formulation variations as shown in Tables 5 and 6.

**Table 5.** Results of physical appearance, gelling capacity and viscosity determination.

| Batch code | Physical appearance | Gelling capacity | Viscosity (cps)* |
|---|---|---|---|
| **LF1** | Milky white | + + | 267.8±12.4 |
| **LF2** | Milky white | + + | 298.4±14.2 |
| **LF3** | Milky white | + + | 189.2±9.8 |
| **LF4** | Milky white | + + | 174.8±8.9 |
| **LF5** | Milky white | + + + | 243.4±11.6 |
| **LF6** | Milky white | + + + | 234.5±11.2 |
| **LF7** | Milky white | + + | 153.8±7.8 |
| **LF8** | Milky white | + + + | 223.7±10.8 |
| **LF9** | Milky white | + + + | 278.2±13.1 |

(+) = weak, (++) = moderate, (+++) = strong

**Table 6.** Results of floating lag time, total floating time and drug content determination.

| Batch code | pH | Floating lag time (s) | Total Floating Time (h) | Drug content (%) |
|---|---|---|---|---|
| **LF1** | 6.6±0.2 | 22.33±1.5 | 7.3±0.4 | 84.32±2.14 |
| **LF2** | 6.5±0.1 | 21.12±1.32 | 6.8±0.2 | 89.61±1.98 |
| **LF3** | 6.7±0.2 | 24.19±1.56 | 7.1±0.4 | 87.57±2.05 |
| **LF4** | 7.2±0.1 | 19.0 ±1.2 | 6.5±0.2 | 91.29±1.87 |
| **LF5** | 6.6±0.2 | 18.03±2.18 | 6.3±0.3 | 93.04±1.76 |
| **LF6** | 6.8±0.1 | 22.04±1.38 | 6.2±0.4 | 91.24±1.89 |
| **LF7** | 7.3±0.2 | 20.68±1.29 | 7.4±0.4 | 77.02±2.34 |
| **LF8** | 7.1±0.1 | 19.33±1.25 | 7.2±1.0 | 79.57±2.21 |
| **LF9** | 7.1±0.2 | 23.46±1.42 | 7.4±0.5 | 73.69±2.45 |

All formulations (LF1–LF9) exhibited a milky white appearance, ensuring uniformity in physical characteristics. Gelling capacity varied among batches, with LF1, LF2, LF3, LF4, and LF7 showing moderate gel strength (++), forming gels immediately and remaining buoyant for 6-7 hours, whereas LF5, LF6, LF8, and LF9 exhibited stronger gel strength (+++), remaining buoyant for more than 6 hours. Viscosity ranged from 153.8 ± 7.8 cps (LF7) to 298.4 ± 14.2 cps (LF2), with higher viscosity formulations (LF5, LF6, LF8, LF9) correlating with enhanced gel strength and better retention.

Floating behavior analysis showed that floating lag time varied between 18.03 ± 2.18 s (LF5) and 24.19 ± 1.56 s (LF3), indicating rapid buoyancy across formulations. The total floating time ranged from 6.2 ± 0.43 hours (LF6) to 7.4 ± 0.52 hours (LF9, LF7), suggesting prolonged gastric retention, essential for gastro-retentive drug delivery.

Drug content ranged from 73.69 ± 2.45% (LF9) to 93.04 ± 1.76% (LF5), with LF5 and LF4 exhibiting the highest drug incorporation efficiency. In contrast, LF7, LF8, and LF9 displayed relatively lower drug content, possibly due to variations in drug distribution. Overall, LF5 emerged as the most promising formulation, demonstrating strong gelation (+++), rapid floating (18.03 sec), prolonged retention (6.3 hours), and high drug content (93.04%), making it an ideal candidate for further optimization in gastro-retentive drug delivery systems.

### 3.6. Optimization of formulation

The ANOVA analysis confirmed the significant impact of gellan gum (A) and calcium carbonate (B) on floating lag time (Y1) and in-vitro drug release (Y2) in gastro-retentive in-situ gel formulations. Results of ANOVA are indicated in Tables 7 and 8. The quadratic model for Y1 ($p = 0.0022$, $F = 79.63$, $R^2 = 0.9925$) showed that gellan gum increased floating lag time, while calcium carbonate reduced it, with significant quadratic effects. For Y2 ($p = 0.0014$, $F = 107.07$, $R^2 = 0.9944$), calcium carbonate played a dominant role in reducing drug release, while gellan gum had minimal influence. The interaction (AB) was significant for Y2 but not for Y1, indicating distinct formulation behaviour. The high $R^2$ values, as shown in Table 9, low SD, and close agreement between adjusted and predicted $R^2$ values confirmed the model's reliability. Optimizing gellan gum and calcium carbonate concentrations is crucial for achieving rapid floating and controlled drug release, ensuring effective gastro-retentive drug delivery.

**Table 7.** ANOVA for quadratic model for floating lag time (Y1).

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|---|---|---|---|---|---|
| **Model** | 34.02 | 5 | 6.80 | 79.63 | 0.0022 |
| A-Gellan gum | 9.60 | 1 | 9.60 | 112.38 | 0.0018 |
| B-Cal. Carbonate | 2.90 | 1 | 2.90 | 33.92 | 0.0101 |
| AB | 0.2116 | 1 | 0.2116 | 2.48 | 0.2136 |
| $A^2$ | 12.22 | 1 | 12.22 | 143.01 | 0.0013 |
| $B^2$ | 9.09 | 1 | 9.09 | 106.37 | 0.0019 |
| **Residual** | 0.2563 | 3 | 0.0854 | | |
| **Cor Total** | 34.27 | 8 | | | |

**Table 8.** ANOVA for quadratic model for in-vitro drug release (Y2).

| Source | Sum of Squares | df | Mean Square | F-value | p-value |
|---|---|---|---|---|---|
| **Model** | 389.75 | 5 | 77.95 | 107.07 | 0.0014 |
| A-Gellan gum | 0.0028 | 1 | 0.0028 | 0.0039 | 0.9543 |
| B-Cal. Carbonate | 162.45 | 1 | 162.45 | 223.14 | 0.0007 |
| AB | 10.82 | 1 | 10.82 | 14.87 | 0.0308 |
| $A^2$ | 20.72 | 1 | 20.72 | 28.45 | 0.0129 |
| $B^2$ | 195.76 | 1 | 195.76 | 268.89 | 0.0005 |
| **Residual** | 2.18 | 3 | 0.7280 | | |
| **Cor Total** | 391.93 | 8 | | | |

**Table 9**. Summary of the quadratic model results for regression analysis of responses R1 and R2.

| Quadratic Model | $R^2$ | Adjusted $R^2$ | Predicted $R^2$ | SD | % CV |
|---|---|---|---|---|---|
| **Response ($Y_1$)** | 0.992 | 0.9801 | 0.9094 | 0.2923 | 21.14 |
| **Response ($Y_2$)** | 0.994 | 0.9851 | 0.9573 | 0.8532 | 1.00 |

### 3.7. Validation of the statistical model

The validation of the statistical model was assessed by comparing the predicted and experimental values of floating lag time and in-vitro drug release for the optimized formulation (LF5). The results, as per table 10, showed minimal relative error between predicted and actual values, confirming the model's accuracy.

For floating lag time, the predicted value (17.899 sec) and experimental value (18.03 sec) showed a relative error of just 0.73%, indicating high precision. Similarly, for in-vitro drug release, the predicted value (93.158%) closely matched the experimental value (93.04%) with a relative error of only 0.13%, demonstrating the model's reliability in predicting formulation behaviour. These findings validate the effectiveness of the quadratic model in optimizing floating lag time and drug release, ensuring robust and reproducible formulation performance.

### 3.8. Results of *in-vitro* drug release and stability study

The in-vitro drug release profile of the gastro-retentive in-situ gel demonstrated a controlled and sustained release pattern, ensuring prolonged drug availability. Figure 6 shows the in-vitro drug release profiles of the formulated gastro-retentive in-situ gel.

The stability study of the optimized batch (LF5) under accelerated conditions (40 ± 2°C, 75 ± 5% RH) for six months confirmed the formulation's stability. Throughout the study, floating lag time remained consistent (18.03 to 17.98 sec), total floating time was maintained (>6 hours), and drug content showed negligible variation (93.04% to 93.00%), indicating no significant degradation. The pH remained within an acceptable range (6.6 to 6.3), ensuring formulation integrity. Additionally, in-vitro drug release showed minimal change (93.198% initially to 93.149% at six months), confirming physical, chemical, and functional stability over time. These results validate the optimized formulation's robustness, ensuring its long-term efficacy and suitability for pharmaceutical applications.

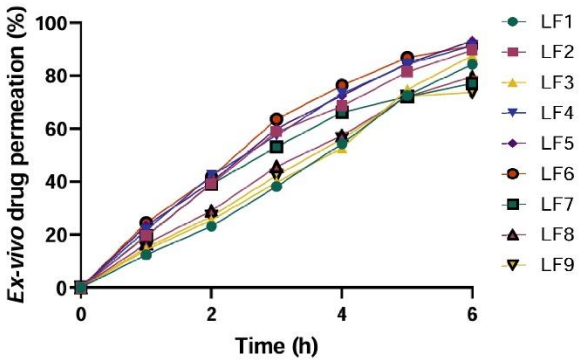


**Fig. 6.** In-vitro drug release profile of gastro-retentive in-situ gel.

## 4. Discussion

### 4.1. Calibration curve and solubility study

The calibration curve of misoprostol in ethanol demonstrated a linear relationship between absorbance and concentration with a high $R^2$ value of 0.9987, confirming the method's reliability for drug quantification. The solubility study revealed that misoprostol is practically insoluble in water (0.023 ± 0.002 mg/ml) but highly soluble in ethanol (49.36 ± 2.72 mg/ml) and DMSO (50.87 ± 2.29 mg/ml), with moderate solubility in phosphate buffer pH 6.8 (1.63 ± 0.41 mg/ml). These findings indicate that misoprostol is hydrophobic, and gastroprotective gels can retain the drug for prolonged period of time giving sustained effect [31].

### 4.2. FTIR and DSC analysis

FTIR spectra of pure misoprostol showed characteristic peaks at 3435 $cm^{-1}$ (-OH stretching), 1732 $cm^{-1}$ (C=O stretching), and 1256 $cm^{-1}$ (-O- stretching), confirming its structural integrity. In the physical mixture, these peaks remained unchanged, with minor shifts, indicating no significant chemical interactions between the drug and excipients.

**Table 10. The predicted and experimental values of response variables and relative error.**

| F. Code | Composition | Actual (mg) | Response | Predicted value | Experimental value | Relative Error (%) |
|---|---|---|---|---|---|---|
| **LF5** | Gellan gum | 1 | Floating lag time (Sec) | 17.899 | 18.03 | 0.73 |
| | Cal. carbonate | 1.5 | | | | |
| **LF5** | Gellan gum | 1 | *In-Vitro* drug release | 93.158 | 93.04 | 0.13 |
| | Cal. carbonate | 1.5 | | | | |

The DSC thermogram of misoprostol exhibited a sharp endothermic peak at 163.07°C, corresponding to its melting point and crystalline nature. The physical mixture showed additional peaks at 90°C and 262°C, indicating partial interaction with excipients while maintaining the drug's crystalline structure.

### 4.3. Physicochemical characterization of gastro-retentive in-situ gel

The pH values (6.5 to 7.3) confirmed compatibility with gastric conditions, ensuring minimal irritation upon administration. Floating lag time ranged between 18.03 to 24.19 seconds, ensuring rapid buoyancy, while total floating time was maintained between 6.2 to 7.4 hours, allowing prolonged gastric retention. Drug content analysis confirmed batch-to-batch consistency, with values ranging between 73.69% and 93.04%, ensuring uniform drug distribution within the gel. The optimized batch (LF5) exhibited 93.04% drug release at 240 minutes, closely aligning with the predicted value of 93.158%. The gelation capacity assessment confirmed strong and stable gel formation, while viscosity analysis ensured adequate consistency for controlled drug diffusion [32].

### 4.4. Optimization using $3^2$ Factorial Design

The effect of gellan gum ($X_1$) and calcium carbonate ($X_2$) on floating lag time ($Y_1$) was optimized using a $3^2$ factorial design. ANOVA results ($p = 0.0022$) confirmed the statistical significance of the model, with gellan gum ($p = 0.0018$) and calcium carbonate ($p = 0.0101$) significantly influencing floating lag time. The regression equation demonstrated that higher gellan gum levels increased floating lag time, whereas calcium carbonate reduced it, confirming its role as a gas-generating agent. The contour plot (Fig. 7A) and 3D surface plot (Fig. 7B) confirmed that floating lag time increased with Gellan gum concentration, reaching a maximum of 24.19 seconds.

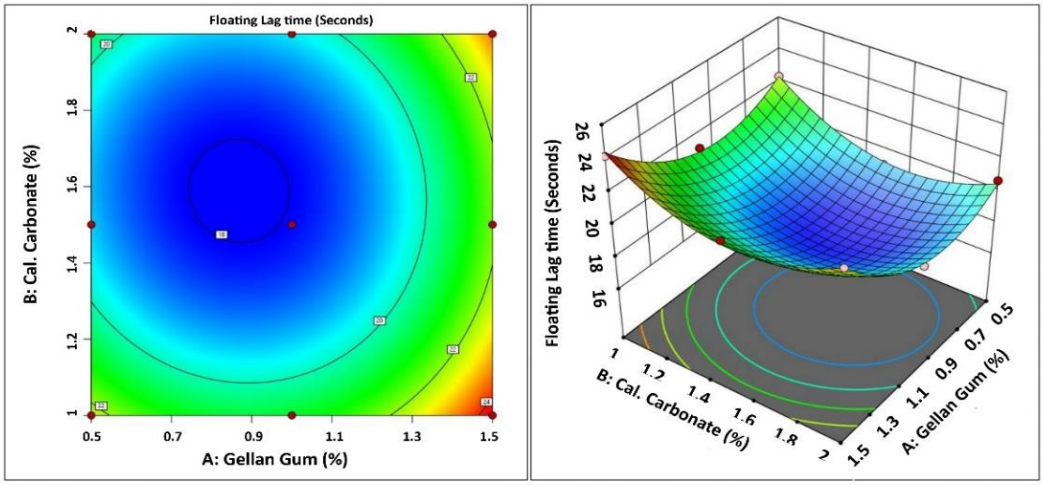


**Fig. 7.** Contour plot (A) and 3D surface plot (B) for the effect of gellan gum and calcium carbonate on floating lag time (Y1) of gastroretentive in-situ gel

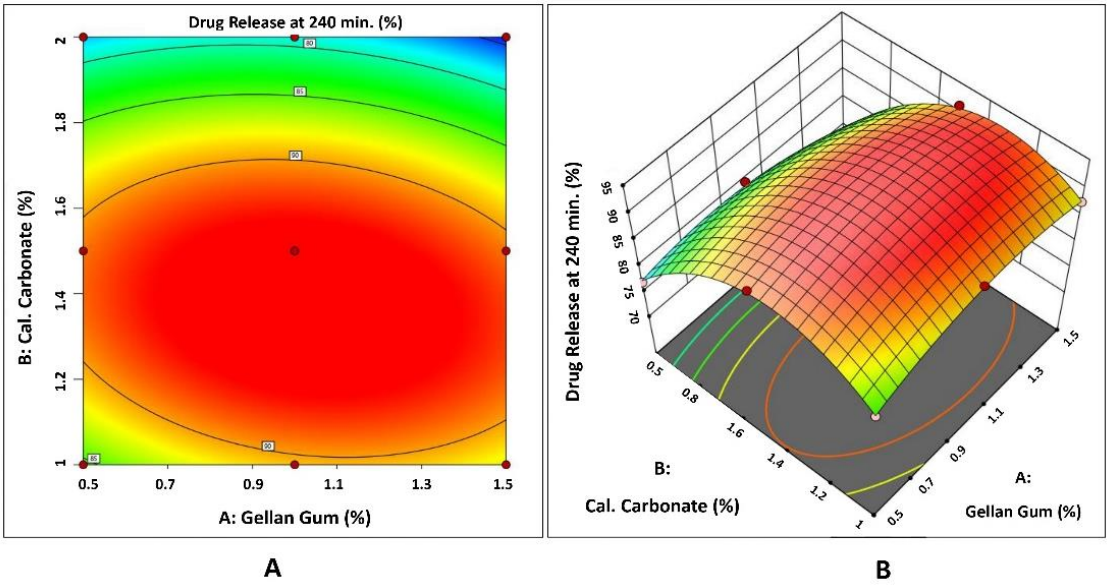


**Fig. 8.** Contour plot (A) and 3D surface plot (B) for the effect of gellan gum and calcium carbonate on in-vitro drug release (Y2) of gastro-retentive in-situ gel.

### 4.5. Impact on in-vitro drug release ($Y_2$)

ANOVA results (p = 0.0014) confirmed the statistical significance of the quadratic model. Calcium carbonate (p = 0.0007) had the most significant effect on drug release, while gellan gum (p = 0.9543) showed minimal influence. Interaction effects (AB = 0.0308) were significant, indicating that both variables play a role in modulating drug release.

Higher-order effects ($B^2$, p = 0.0005) demonstrated a non-linear impact, suggesting that excess calcium carbonate may slightly alter the release pattern. The contour plot (Fig. 8A) and 3D surface plot (Fig. 8B) confirmed that drug release increased significantly with higher calcium carbonate levels, reaching 93.04% at 240 minutes.

### 4.6. Optimization & model validation

The predicted in-vitro drug release (93.158%) closely matched the experimental value (93.04%), confirming the model's reliability. Calcium carbonate played a crucial role in drug diffusion, effervescence, and buoyancy, while gellan gum contributed to gel stability. The quadratic model successfully optimized response variables, confirming its application in developing gastro-retentive in-situ gels for misoprostol delivery.

### 4.7. Stability study

The optimized batch (LF5) was subjected to accelerated stability studies (40 ± 2°C, 75 ± 5% RH for six months). The floating lag time (18.03 sec), total floating time (>6 hours), drug content (>93%), and in-vitro drug release (93.198% to 93.149%) remained consistent, confirming formulation stability. These findings suggest that the developed gastro-retentive in-situ gel is stable, retaining its controlled-release properties, making it suitable for long-term storage and clinical applications [33].

## 5. Conclusion

The study successfully developed and optimized a gastro-retentive in-situ gel formulation of misoprostol, addressing the limitations of conventional oral delivery. The optimized formulation exhibited rapid buoyancy, sustained gastric retention, and controlled drug release, with the floating lag time at 18.03 seconds and drug release of 93.04% over 240 minutes.

Statistical analysis confirmed that calcium carbonate significantly influenced drug release, while gellan gum played a critical role in gelation and structural stability. Stability studies demonstrated no significant changes in formulation parameters over six months, confirming its robustness for long-term use. These findings establish gastro-retentive in-situ gel as a viable drug delivery system, enhancing the therapeutic potential of misoprostol for effective peptic ulcer management.

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